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review

ATM and ataxia telangiectasia

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Ataxia telangiectasia (AT) has long intrigued the biomedical research community owing to the spectrum of defects that are characteristic of the disease, including neurodegeneration, immune dysfunction, radiosensitivity and cancer predisposition. Following the identification of mutations in *ATM* (ataxia telangiectasia, mutated) as the underlying cause of the disease, biochemical analysis of this protein kinase has shown that it is a crucial nexus for the cellular response to DNA double-stranded breaks. Many ATM kinase substrates are important players in the cellular responses that prevent cancer. Accordingly, AT is a disease that results from defects in the response to specific types of DNA damage. Thus, although it is a rare neurodegenerative disease, understanding the biology of AT will lead to a greater understanding of the fundamental processes that underpin cancer and neurodegeneration.

Keywords: ataxia telangiectasia; ATM; DNA damage; neurodegeneration

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Introduction

Ataxia telangiectasia (AT) is a neurodegenerative disease that occurs early in childhood (Gatti *et al*, 2001; Sedgwick & Boder, 1991). Clinically, AT presents with uncoordinated or ataxic movements that are often associated with ocular telangiectasia (dilated blood vessels of the eye). One certain outcome of AT is that an individual will be wheelchair-bound early in life, almost always before the adolescent years. The prominent neurological sign of AT is an inexorable loss of cerebellar function, and progressive dysarthria (speech defects) and choreoathetosis (abnormal body movements; Crawford, 1998; Gatti *et al*, 2001; Sedgwick & Boder, 1991). Autopsies and magnetic resonance imaging (MRI) studies have revealed significant thinning of the molecular layer of the cerebellum and cerebellar atrophy, especially in vermal regions (Farina *et al*, 1994; Tavani *et al*, 2003). Characteristic eye movement abnormalities (distinct from telangiectasia) also feature strongly in AT, and these might be related to cerebellar dysfunction (Lewis *et al*, 1999). Although substantial advances have recently been made in the clinical diagnosis of this disease, treatments for the progressive neurodegeneration are lacking (Perlman *et al*, 2003).

In addition to the hallmark neurodegeneration, there are a number of other features that typify this debilitating disease. These include immune dysfunction, sterility, radiosensitivity and lymphoid cancer (Fig 1). The immunodeficiency phenotype in AT is variable

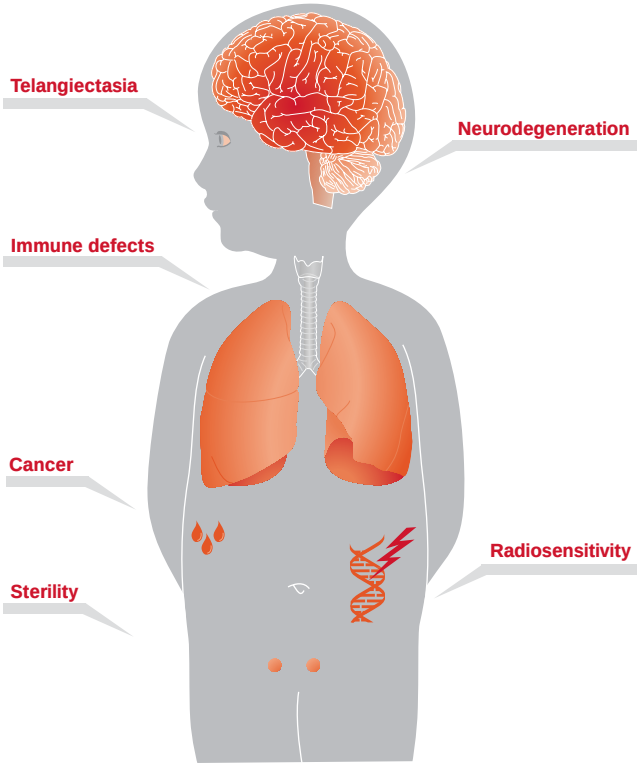

Fig 1 | Ataxia telangiectasia. Ataxia telangiectasia (AT) is a multisystem syndrome that results from the mutation of *ATM* (ataxia telangiectasia, mutated); the hallmark of clinical presentation is a debilitating progressive neurodegeneration. Other characteristics are extreme radiosensitivity, immunodeficiency, a predisposition to cancer (haematopoietic malignancy) and sterility due to defective meiotic recombination. Ocular and facial telangiectasia are also associated with AT.

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and usually manifests as decreased or absent IgA, IgE and IgG2, although severe bacterial or viral opportunistic infections are rare (Nowak-Wegrzyn *et al*, 2004). The cause of death in AT is often pneumonia or chronic lung disease, which might result from defects in chewing and swallowing owing to progressive neurological impairment (Lefton-Greif *et al*, 2000; Nowak-Wegrzyn *et al*, 2004). Cancer predisposition is due to an increased susceptibility to lymphoreticular disease such as leukaemia and lymphoma (Gumy-Pause *et al*, 2004). *ATM* mutations have also been linked to breast cancer (Angele *et al*, 2003; Thorstenson *et al*, 2003). Thus, understanding the molecular basis for AT will yield important biological insights linking a diverse group of pathologies such as neurodegeneration, immune deficiency and cancer.

Dysfunction of the ATM kinase is responsible for AT

A major breakthrough in understanding AT came with the identification of a single gene, *ATM* (ataxia telangiectasia, mutated), which when mutated is the underlying cause of the disease (Savitsky *et al*, 1995). Indeed, as such a broad spectrum of organs are affected in AT, the discovery of *ATM* was hailed as a medical equivalent of the Rosetta stone (Nowak, 1995). The identification of *ATM* has facilitated rapid progress in understanding many aspects of the molecular basis of this disease.

ATM has sequence homology to a family of proteins that are related to the phosphatidylinositol-3-OH-kinases (PI(3)K), although ATM is a protein kinase rather than a lipid kinase (Fig 2). ATM is a large protein; the genomic DNA contains 66 exons resulting in an mRNA of approximately 12 kb that encodes a protein of approximately 350 kDa. Mutations identified in *ATM* occur throughout the gene with no 'hot spots' and generally lead to protein instability (Lakin *et al*, 1996; Sandoval *et al*, 1999). Some mutations result in the production of decreased amounts of functional protein, or normal amounts with markedly reduced kinase activity. These mutations cause a milder version of AT with a less severe clinical phenotype, although neurodegeneration is still present (Stewart *et al*, 2001). A detailed *ATM* mutation database can be found at http://www.vmresearch.org/bri_investigators/atm.htm.

ATM is a protein kinase that responds to DNA damage

ATM is the apex of a signalling cascade that responds to DNA double-stranded breaks (DSBs) and is key to coordinating the resulting cellular response (Shiloh, 2003). It is also required for processing the physiological DNA strand breaks that occur during meiosis, immune system maturation and for telomere maintenance. ATM is a serine–threonine protein kinase that undergoes autophosphorylation after DNA damage to subsequently initiate a signalling cascade that involves the phosphorylation of several substrates (Kastan & Lim, 2000; Shiloh, 2003). Many ATM substrates are cell-cycle regulators that have essential functions in the cellular response to DNA damage and include p53, breast-cancer-associated 1 (BRCA1), p53-binding protein 1 (53BP1) and the checkpoint kinase CHK2. The response to DNA damage appears to be the primary, if not the definitive, function of this kinase.

Recently, substantial insight has been achieved regarding the mechanism by which ATM signals that DNA has been damaged (Fig 3). In response to DSBs, ATM is autophosphorylated at Ser-1981, which leads to the dissociation of inactive multimeric ATM (either a dimer or higher order multimer) to initiate ATM signalling (Bakkenist & Kastan, 2003). Although ATM is essential for the DSB response, it functions in concert with other factors. Foremost among these is the MRN complex (Carson *et al*, 2003; Uziel *et al*, 2003), named as such because of its three principal component proteins: MRE11, RAD50 and NBS1 (D'Amours & Jackson, 2002; Petrini & Stracker, 2003; van den Bosch *et al*, 2003). Activated ATM can directly associate with the MRN complex, and this interaction can control signalling by influencing the ATM substrate choice (Lee & Paull, 2004). Indeed, the important inter-relationship between ATM and the MRN complex is underscored by the similarity of two other syndromes related to AT that result from hypomorphic mutations in NBS1 and MRE11; Nijmegen breakage syndrome and AT-like disorder (discussed later).

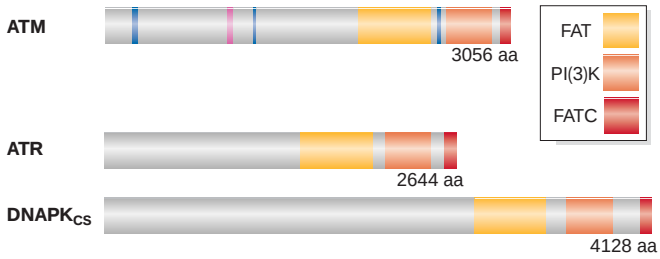

Fig 2 | The structure of ATM. Ataxia telangiectasia, mutated (ATM) is a large protein that has carboxy-terminal similarity to other proteins of the phosphatidylinositol-3-OH-kinase (PI(3)K) family. Two other representative protein kinases—ATM-Rad3 related (ATR) and the catalytic subunit of the DNA-dependent protein kinase ($DNAPK_{cs}$)—are included for comparison. Each of these PI(3)K members contain similar domains: a FAT domain, so named because it is a common motif in other related proteins, including FRAPP/ATM/TRRAP; the PI(3)K domain that was initially used to assign ATM to the PI(3)K family; and a FATC domain that represents a common C-terminal amino-acid sequence found near the termini of the protein. The blue lines indicate nuclear localization signals and the pink line indicates a leucine zipper region within ATM.

In addition to ATM and MRN, other key players in the DSB response include histone H2AX, 53BP1, mediator of damage checkpoint 1 (MDC1) and BRCA1. These factors are all substrates of ATM. After DNA damage, these factors rapidly mobilize to the sites of DSBs and initiate an ATM-dependent signalling cascade that leads to the resolution of the break through DNA repair, or, in the case of excessive DNA damage, cell death, often through p53-mediated apoptosis. Collectively, these proteins function as key regulators of the DNA damage response, and a clear interdependency exists among them as inactivation of any of them renders cells hypersensitive to DSBs (Kitagawa *et al*, 2004; Petrini & Stracker, 2003; Sedelnikova *et al*, 2003; Shiloh, 2003; van den Bosch *et al*, 2003). Thus, ATM signalling after DSBs involves a coordinated series of events that occur rapidly and collectively serve to activate key cellular effectors (Shiloh, 2003).

ATM controls cell-cycle checkpoints

A crucial survival function when DSBs occur is the inhibition of the cell cycle through the activation of cell-cycle checkpoints. Checkpoints occur to introduce a pause in proliferation to address cellular stress. Although checkpoints can be easily demonstrated in cell-culture systems, the occurrence and role of these *in vivo* are less clear. However, the proteins that influence checkpoints are often required to prevent cancer.

Factors involved in DNA damage responses are intimately linked to the activation of checkpoints. Because many ATM substrates are key effectors of the cell cycle, cells derived from AT individuals have defective cell-cycle checkpoints. For example, p53 is required for the G1 and CHK2 for the G2 DNA damage-induced checkpoints, whereas proteins such as BRCA1 and NBS1 control the intra-S phase checkpoint. Therefore, the defective cell-cycle checkpoints present in AT cells after DNA damage represent the defective phosphorylation of ATM substrates (Motoyama & Naka, 2004; Shiloh, 2003).

ATM and cancer

Cancer is linked to genomic instability and, consequently, many individuals suffering from syndromes that are characterized by defects in DNA damage responses are also cancer prone (Hoeijmakers, 2001; van Gent *et al*, 2001). Cancer occurs in about 10% of AT individuals and reflects the central role of ATM in the response to DSBs. However, despite the nervous system being markedly affected in AT, the tumour types occurring in this disease are primarily lymphoma or leukaemia (Gumy-Pause *et al*, 2004). Typical cytogenetic changes seen in tumours from AT individuals often involve aberrant oncogenic rearrangements at the T-cell receptor loci. The occurrence of these tumours underscores the requirement for ATM to ensure high-fidelity immunoglobulin-gene recombination after the normal DNA breakage and processing that occurs during immune system maturation (Liao & Van Dyke, 1999; Perkins *et al*, 2002).

Somatic mutations in *ATM* have been identified in some sporadic cancers, particularly leukaemias (Boultwood, 2001; Stankovi *et al*, 2002; Thorstenson *et al*, 2003). Additionally, a substantial body of work has linked *ATM* heterozygotes to cancer predisposition (Angele *et al*, 2003; FitzGerald *et al*, 1997; Thorstenson *et al*, 2003). Recently, it has been shown that the nature of the particular ATM mutation has a substantial bearing on ATM heterozygote cancer susceptibility, as some mutant versions of ATM can act in a dominant interfering manner to partially disrupt ATM signalling (Spring *et al*, 2002).

ATM, neurodegeneration and DNA damage

The hallmark of AT is neurodegeneration. Understanding how dysfunctional ATM has an impact on the nervous system will first involve understanding the ATM signalling pathway in the brain and the aetiological agent that underlies the neurodegeneration. A clear picture of ATM function in the nervous system has yet to emerge, although substantial evidence supports a causal role in responding to DNA damage. Many human syndromes associated with DNA repair deficiencies also show neurological defects (Caldecott, 2003; Rolig & McKinnon, 2000), which indicates that proper DNA damage responses are crucial for homeostasis of the nervous system.

Genetic insight into the requirement for DNA repair during nervous system development was initially obtained in mice in which the DNA ligase IV (Lig4) or the X-ray repair cross-complementing protein (XRCC4) had been deleted (Barnes *et al*, 1998; Gao *et al*, 1998). Inactivation of either of these partner proteins leads to mid-gestational embryonic lethality and is associated with abundant apoptosis throughout the entire neuraxis. Inactivation of other DNA repair genes have further established the broad requirement for DNA damage responses during development (Abner & McKinnon, 2004).

The early initiating events that involve ATM activation are likely to be similar in the nervous system to those described *in vitro*. However, in the nervous system, ATM response to DNA damage shows some important context dependency, and it is likely that the specific types of DNA damage, and the nature of the cell type incurring this damage, are important determinants of ATM signal transduction (Borges *et al*, 2004; Herzog *et al*, 1998; Lee *et al*, 2001). ATM has been implicated directly in the response to endogenous damage in the nervous system as DNA lesions arising from Lig4 deficiency activate ATM to initiate neural apoptosis, and in Lig4/Atm double-null mice, apoptosis is abrogated (Lee *et al*, 2000; Sekiguchi *et al*, 2001). One function of ATM in the nervous system, therefore, is to eliminate neural cells that incur DNA damage, and failure to do this might lead to the accumulation of genetic lesions that eventually compromise cellular function and viability, causing cell death. Thus, DNA damage responses that engage ATM signalling are important in ensuring that genotoxic stress is relieved during neural development.

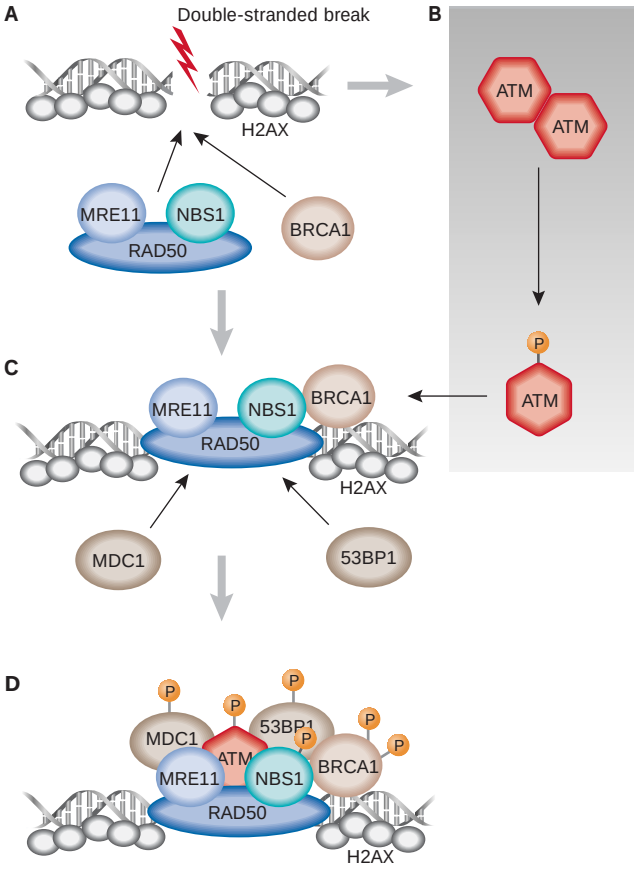

Fig 3 | ATM and DNA damage signalling. In response to a DNA double-stranded break (**A**) several simultaneous events occur to ultimately activate ATM signal transduction. ATM exists as an inactive multimeric complex that, in response to DNA damage, undergoes autophosphorylation to an active monomer (**B**). A histone variant, histone H2AX, present within chromatin, becomes phosphorylated and serves as a tethering platform for repair factors. The MRE11–RAD50–NBS1 complex locates to the DNA lesion together with BRCA1 (**C**). Assembly of this complex facilitates coordinated co-localization of active ATM together with other factors including MDC1/NFBD1 and 53BP1. BRCA1, MDC1 and 53BP1 are also phosphorylated in an ATM-dependent manner (**D**). The assembly of this multiprotein complex facilitates the cellular response to a DNA double-stranded break. 53BP1, p53-binding protein 1; ATM, ataxia telangiectasia, mutated; BRCA1, breast-cancer-associated 1; MDC1, mediator of damage checkpoint 1.

Ataxia-telangiectasia-related disorders

Of particular relevance to DNA damage and AT are certain hypomorphic mutations of *MRE11* that lead to a similar disease called ATLD. These individuals are also characterized by neurodegeneration, albeit less severe than AT (Stewart *et al*, 1999). In addition, mutations in *NBS1*, an ATM substrate that is involved in the DNA damage-induced intra-S phase checkpoint, lead to the Nijmegen breakage syndrome (NBS), which is a disease phenotypically similar to AT but with distinct neurological defects (Carney *et al*, 1998; Shiloh, 1997; Varon *et al*, 1998). In NBS, microcephaly is the neurological hallmark, rather than the progressive neurodegeneration that is seen in AT. The different ATLD and NBS neural phenotypes suggest some differential requirements for NBS1 and MRE11 function in the nervous system. It is unclear how the principal signalling pathways that involve this multiprotein complex might function differently in nervous system development than in other tissues; the microcephaly characteristic of NBS compared with the neurodegeneration of ATLD suggest that MRN-ATM function is subject to other regulatory mechanisms in the nervous system. Recently, *in vitro* biochemical analyses have suggested independent functions for the MRN complex and a complex of only MRE11 and RAD50 (MR) that involve the selective activation of different ATM substrates. In this scenario, ATM activation by the MR complex activates p53, whereas the binding of ATM to the MRN complex activates CHK2 (Lee & Paull, 2004).

The case for DNA damage as a primary factor in AT-associated neurodegeneration is strong, but increased oxidative stress resulting from ATM deficiency in the nervous system has been reported, although the mechanism for this feature is unclear (Barlow *et al*, 1999; Kamsler *et al*, 2001; Quick & Dugan, 2001). Whether this is a primary or secondary effect of ATM deficiency is also not known.

Conclusions

Is DNA damage a common denominator for the AT phenotype? The simplest interpretation for the role of ATM in preventing AT is that it ensures an appropriate response to DNA damage. This aspect of ATM function explains the immune-system defects that require gene rearrangements for immune maturation, and also the development of lymphoma or leukaemia. Radiosensitivity is also clearly linked to a defective DNA damage response, and sterility results from defects early in meiosis that involve genetic recombination events (Barlow *et al*, 1997). However, some features, such as ocular telangiectasia and insulin resistance, are more difficult to reconcile with a defective DNA damage response.

It has been most difficult to assign a molecular basis to neurodegeneration. This is largely because of the relative difficulty of working with neural tissues and neuronal cultures compared with standard culture approaches using transformed cells. However, defective DNA damage responses underlie the molecular basis of other neurodegenerative syndromes that are characterized by ataxia similar to AT. In fact, the most common recessive ataxia in Japan and the second most common in Portugal (after Friedrich's ataxia)—ataxia-ocular apraxia 1—has very similar neuropathology to AT. It results from mutations in aprataxin, which is a protein that is involved in the response to single-stranded breaks in DNA rather than DSBs (Date *et al*, 2001; Gueven *et al*, 2004; Moreira *et al*, 2001). It is likely that an increasing number of uncharacterized ataxias and neurological diseases will be shown to be the result of inappropriate responses to DNA damage.

Whereas a great deal of insight has come from studies with AT cells, there is still much that is unresolved about ATM function. An important undertaking will be to integrate the biochemical signalling involving the numerous substrates of ATM into a cohesive biological picture that accounts for the pleiotropic AT phenotype. In particular, it will be important to understand the molecular basis of the tissue-specific functions of ATM in responding to DNA damage (Baker & McKinnon, 2004). For example, why are some tissues, such as the haematopoietic and intestinal tract, hypersensitive to DNA-damage-induced cell death when ATM is dysfunctional, whereas other organs, such as the developing brain, are resistant? How does the resistance of immature neural cells to DNA-damage-induced cell death relate to neurodegeneration; do these cells subsequently die from accumulated genetic lesions? Understanding tissue-specific ATM function will provide important insights into context-dependent consequences of DNA damage that will have broad biological implications.

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